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Dear Josh,

Very many thanks for your letter. Science of 19th June arrived between my writing and your reply, and I read your article with the utmost pleasure and interest. Whatever else may turn out right or wrong in it, I feel convinced of the essential truth of the elective theory. As your propositions are proposals rather than assertions there is nothing to quarrel with - things will sort themselves out in time. Three points come to mind which I'd like you to comment on sometime.

1. I don't see how A3, according to which genetic variants among antibody forming cells arise randomly, provides for the possibility that certain individual animals may be incapable of forming antibodies against particular determinant groups. Here see some wise and informative remarks by Eisen, pp. 645-649 in "Cellular and humoral aspects of hypersensitive states", ed. H.S.Lawrence, Hoeber 1959. Indeed, I don't see at the moment how to reconcile A3 with the possibility that immunological performance may mendelize in the manner hinted at by the data in your ref (33). If you write some additional notes to accompany the reprint of your paper, I hope therefore you will amplify the last para. of A4.

Incidentally, Avrion's paper at Royaumont called attention to the extraordinary speed with which normal reactivity returns to formerly tolerant animals after antigen has expired. This argues for a high mutation rate among immunologically competent cells. On the other hand one has to remember that Jim Gowans's new work on the longevity of lymphocytes shows that the mitotic rate in lymphoid tissue has been greatly exaggerated, under the impression that all lymphocytes entering the blood stream are newly formed.

2. What you say about embryonic differentiation in para. 3 of A3 and in the last para of your paper is open to misunderstanding. Burnet explicitly states that the diversification of antibody forming cells is due to the same kind of process as that which occurs in embryonic differen-

tiation generally. You refer to "a specific mechanism of cellular differentiation" in para. 3 of A3. I'm almost sure you mean that the diversification of lymphoid cells is one among several possible kinds of differentiation — not that A3 provides a specific explanation of embryonic differentiation.

It strikes me that Burnet's belief that somatic mutation accounts for embryonic differentiation generally is inherently paradoxical. For, here, the mutations must be orderly and not random. If they are orderly, the zygote must contain enough information to ensure that the right mutations occur at the right time, place and order. But if the zygote contains this wealth of information anyway, it becomes pointless to bring in somatic mutation in order to enlarge it. I'm all for differentiation being an elective process but still have to be convinced that there isn't enough information in the zygote to subsidize it.

3. A fascinating news item occurs on p. 179 of the Abstracts of the VIIth Int. Congress of Microbiology in Stockholm. You probably know that the intracutaneous injection of diphtheria toxin produces a violent inflammation unless specific antitoxin is present in the subject's blood (Schick test). Milgrom and his colleagues claim to have produced tolerance of diphtheria toxin in guinea pigs in the sense that they* don't produce antitoxin after antigenic challenge — but the interesting and paradoxical point is that these tolerant animals are Schick-negative, i.e. they don't produce the inflammatory response to be expected of animals with no circulating antitoxin.

This is exactly the result one would predict if tolerance were due to induced enzyme formation, as suggested at Royaumont: a specific enzyme is formed which catabolizes toxin too fast for antibody formation and too fast for it to produce dermal necrosis. However, I expect there's a catch somewhere in this explanation!

Don't fail to send a reprint of the Science paper —and apologies for a not very coherent letter.

All good wishes,

Peter.

P.S. I laughed a lot at your lexicographical analysis of entailment. It's a perfectly respectable word in old-fashioned logic — ask an old-fashioned logician, if there are any on the Stanford campus!

*the guinea pigs, not Milgrom et al.